REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

No claims are amended.

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Claims 1-57 are now pending in this application. Claims 1-27 and 33-57 are withdrawn as non-elected. Claims 28-32 are under examination.

I. OATH/DECLARATION

Applicants have submitted herewith a new declaration under 37 C.F.R. § 1.67(a) to replace the defective declaration of record.

II. NOVELTY

Claim 28 stands rejected as anticipated by Shields et al., J. Biol. Chem., 2002, Vol. 277, pages 26733-26740 ("Shields").

Applicants respectfully traverse.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. § 2131 (citing *Verdegaal Bros. v. Union Oil Co. of Calif.*, 814 F.2d 628, 631 (Fed. Cir. 1987). "All words in a claim must be considered in judging the patentability of that claim against the prior art." M.P.E.P. § 2143.03, quoting *In re Wilson*, 424 F.2d 1382, 1385 (C.C.P.A. 1970).

Here, Shields fails to satisfy the limitation "said antibodies have on their glycosylation site of the Fc region, glycanic structures having a fucose content/galactose content ratio less than 0.6". As noted in the specification, "fucose content/galactose content ratio is obtained by

dividing the fucose content by the galactose content" (see paragraph [0114] of publication US 2007-0015239).

Calculating the fucose content/galactose content ratio of the antibodies disclosed in Shields reveals that all are above 0.6. Thus, none of Shields' antibodies has a fucose content/galactose content ratio below 0.6.

We determine the galactose content of the Shields antibodies from Table I (see page 26735). Table I discloses values as a percent of total oligosaccharide (see footnote *b*, line 1, below Table I).

Shields discloses independent lots of Hu4D5 monoclonal antibodies expressed in Lec-13, wherein each has a galactose content (Gal1 + Gal2) of between 5% and 9% when the monoclonal antibodies are also fucosylated (see page 26735, Table I, right column, rows labeled Lec-A to Lec Avg). Shields states that the Hu4D5 monoclonal antibodies expressed in Lec13 cells "consistently had about 10% fucosylated carbohydrate (Table I)". See page 26734, right column, lines 1-3 below "RESULTS". Accordingly, for calculating the fucose content/galactose content ratio of the Shields antibodies, we use fucose content of 10%.

For Hu4D5 monoclonal antibodies, the fucose/galactose content ratio can be calculated using the galactose content data in Table I (for "Gal1" and "Gal2") and the fucose content of 10% for the antibodies expressed in Lec13 cells (page 26734, right column, Table 1, under the heading "With fucose"). We calculate as follows from Table I:

- For Lec-A, Gal1 = 4 and Gal2 = 2, so the fucose content/galactose content ratio is **1.66** (10% fucose content/6 % galactose content = 1.66).
- For Lec-B, Gal1 = 4 and Gal2 = 2, so the fucose content/galactose content ratio is **1.66** (10% fucose content/6 % galactose content = 1.66).
- For Lec-C, Gal1 = 4 and Gal2 = 1, so the fucose content/galactose content ratio is **2** (10% fucose content/5 % galactose content = 2).

- For Lec-D, Gal1 = 7 and Gal2 = 2, so the fucose content/galactose content ratio is **1.1** (10% fucose content/9 % galactose content = 1.1).

- For Lec-E, Gal1 = 6 and Gal2 = 1, so the fucose content/galactose content ratio is **1.4** (10% fucose content/7 % galactose content = 1.4).

- For Lec-F, Gal1 = 6 and Gal2 = 2, so the fucose content/galactose content ratio is **1.25** (10% fucose content/8 % galactose content = 1.25).

- For Lec-Avg, Gal1 = 5 and Gal2 = 2, so the fucose content/galactose content ratio is **1.4** (10% fucose content/7 % galactose content = 1.4).

Thus, all of the fucose content/galactose content ratios disclosed in Shields for Hu4D5 monoclonal antibodies are above 0.6. Shields discloses fucose content/galactose content ratio between 1.1 and 2 with an average of 1.4. None has a fucose content/galactose content ratio below 0.6.

As to the Hu4D5 monoclonal antibodies expressed in CHO-S or CHO-P, Shields discloses these have 98% fucose (page 26734, right column, lines 3-6 below "RESULTS"). In Table I, Shields discloses that these antibodies have 48% or 28% of galactose. Specifically, Shields discloses 42% Gal1 + 6% Gal2 for CHO-S and , 25% Gal1 + 3% Gal2 for CHO-P. See Table I, rows 2-3). The fucose/galactose ratio is at least 2 for both, i.e., 98%/48% = 2 for CHO-S, and 98%/28% = 3.5 for CHO-P. In both cases, the ratio is not below 0.6.

As to the HuE27 monoclonal antibodies, Shields states that the percentage without fucose is 2% for CHO-P, 16% for HEK293 and 78% for Lec13 (See page 26735, left column). So the percentage of monoclonal antibodies HuE27 with fucose is respectively:

- 98% for CHO-P (or 100% – 2%)
- 84% for HEK293 (or 100% – 16%)
- 22% for Lec13 (or 100% – 22%)

The following calculations use the percent fucose values shown above and the galactose content data in Table I (for "Gal1" and "Gal2"). The calculations show that none of antibodies has a fucose/galatose ratio less than 0.6.

- For **HEK**-A, Gal1 = 25 and Gal2 = 10 so the fucose content/galactose content ratio is **2.4** (84% fucose content/35 galactose content).
- For HEK-B, Gal1 = 19 et Gal2 = 9 so the fucose content/galactose content ratio is **3** (84% fucose content/28 galactose content).
- For HEK-C, Gal1 = 30 et Gal2 = 15 so the fucose content/galactose content ratio is **1.86** (84% fucose content/45 galactose content)
- For HEK-Arv, Gal1 = 25 et Gal2 = 11 so the fucose content/galactose content ratio is **2.33** (84% fucose content/36 galactose content)
- For HEK-AAA, Gal1 = 17 et Gal2 = 13 so the fucose content/galactose content ratio is **2.8** (84% fucose content/30 galactose content)
- For CHO-P, Gal1 = 26 et Gal2 = 2 so the fucose content/galactose content ratio is **3.5** (98% fucose content/28 galactose content)
- For Lec, Gal1 = 8 et Gal2 = 6 so the fucose content/galactose content ratio is **1.57** (22% fucose content/14 galactose content)

Consequently, none of the monoclonal antibodies described in Shields has a fucose content/galactose content ratio less than 0.6. Shields clearly fails to satisfy the limitation "said antibodies have on their glycosylation site of the Fc region, glycanic structures having a fucose content/galactose content ratio less than 0.6".

Thus, Shields cannot anticipate claim 28, and the rejection should be withdrawn.

III. NON-OBVIOUSNESS

Claims 28-32 stand rejected as anticipated by Shields in view of Shinkawa, et al., J. Biol. Chem., 2003, Vol. 278, pages 3466-3473 ("Shinkawa") and Cartron, et al., Blood, 2002. Vol. 99, pages 754-758 ("Cartron").

Applicants respectfully traverse.

The Office relied on Shields to satisfy the limitation "fucose content/galactose content ratio less than 0.6" as alleged in asserting anticipation. See Office Action, page 6, line 9, and page 7, lines 9-10, 13-14, and 19-20.

"[T]here must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. __, 82 U.S.P.Q.2d 1385, 1391 (2007). "All words in a claim must be considered in judging the patentability of that claim against the prior art." M.P.E.P. § 2143.03, quoting *In re Wilson*, 424 F.2d 1382, 1385 (C.C.P.A. 1970).

Here, absent Shields as basis for satisfying the "fucose content/galactose content ratio" limitation, the Office could not account for this limitation. Thus, the Office could not satisfy its burden to provide the required "articulated reasoning with some rational underpinning" for asserting obviousness.

As explained above in traversing the anticipation rejection, Shields fails to satisfy the "fucose content/galactose content ratio" limitation, because Shields discloses no monoclonal antibodies with "fucose content/galactose content ratio less than 0.6".

Shinkawa and Cartron fail to cure this deficiency. Indeed, the Office did not assert that Shinkawa or Cartron disclose monoclonal antibodies with "fucose content/galactose content ratio less than 0.6".

Further, the Office declined to assert that Shinkawa or Cartron would suggest monoclonal antibodies with "fucose content/galactose content ratio less than 0.6". Fairly considered, neither Shinkawa nor Cartron would have led a skilled artisan to the present invention as claimed.

As explained in the specification, Applicants unexpectedly discovered that there is an inverse relationship between the claimed fucose content/galactose content ratio and ADCC:

> [0011] By studying the full glycoside profile of polyclonal antibodies, we discovered an inverse relationship between the [fucose content/galactose content] ratio and the effector activity of the antibodies.
>
> [0012] Indeed, if the antibody is highly fucosylated, it needs to be highly galactosylated in order to have optimum effector activity. A contrario, if the antibody is slightly fucosylated, the present galactose content should be such that the fucose content/galactose content ratio is less than 0.6 but preferably less than 0.5 or even 0.4 in order to have optimum effector activity.

Shinkawa would have led a skilled artisan away from this discovery, because Shinkawa disclosed that galactose content has no relevance to ADCC. Shinkawa pointedly stated, "we could not find any correlation between the content of Gal and ADCC" (page 3471, right column, lines 10-11 from bottom).

Carton is completely silent regarding the glycosylation profile of monoclonal antibodies.

Taken together, Shields, Shinkawa, and Cartron do not establish a prima facie case of obviousness

Consequently, Applicants request withdrawal of this ground of rejection.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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